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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/579,251

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Luca Gianni

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EXAMINER

LAU, JONATHAN S

ART UNIT

PAPER NUMBER

1623

NOTIFICATION DATE

DELIVERY MODE

04/02/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No. 10/579,251	Applicant(s) GIANNI ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-10 and 12-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-10 and 12-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1 pg / 15 Jan 2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 Jan 2009 has been entered.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 15 Jan 2009, in which claim 1 is amended to change the scope and breadth of the claim.

This application is the national stage entry of PCT/GB04/50025, filed 12 Nov 2004; and claims benefit of foreign priority document UNITED KINGDOM 0326486.8, filed 14 Nov 2003. The foreign priority document is in English.

Claims 1, 3-10 and 12-15 are pending.

Rejections Withdrawn

Applicant's Amendment, filed 15 Jan 2009, with respect to claims 1, 3-10 and 12-15 rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. (WIPO publication WO 02/36135, published 10 May 2002, of record) and Bowman et al. (WIPO

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publication WO 00/69441, published 23 Nov 2000, of record), which is incorporated-by-reference into Takahashi et al. (Takahashi et al. page 1, lines 5-7) in view of Dorr et al. (Cancer Chemotherapy Handbook, 1994, Appleton & Lange, 2nd ed, p395-416, of record) has been fully considered and is persuasive, as amended claim 1 recites the method with ET-743 administered in a dose range between 0.6 and 0.75 mg/m² and Takahashi et al. and Bowman et al. in view of Dorr et al. teaches a dosage of 0.5 mg/m².

This rejection has been **withdrawn**.

The following are new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended Claims 1, 3-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. (WIPO publication WO 02/36135, published 10 May 2002, of record), hereafter WIPO '135, in view of van Kesteren et al. (Clinical Cancer Research, 2000, 6, p4725-4732, cited in PTO-892) and in view of Takahashi et al. (Clinical Cancer Research, 2001, 7, p3251-3257, provided by Applicant in IDS filed 12 May 2006), hereafter "Takahashi et al. 2001", and further in view of Dorr et al. (Cancer Chemotherapy Handbook, 1994, Appleton & Lange, 2nd ed, p395-416, of record).

WIPO '135 discloses the method of combination therapy of ET-743 and doxorubicin to treat the cancer sarcoma (page 2, lines 26-29), specifically envisioning treating a human (page 4, lines 11-12). WIPO '135 discloses the drugs provided as a separate composition for administration at different times (page 1, lines 12-13). WIPO '135 discloses administering ET-743 after administering doxorubicin (page 21, lines 13-14), which is to say administering doxorubicin prior to the administration of ET-743. WIPO '135 discloses administration of the compounds by intravenous infusion, with infusion times of up to 24 hours and 2-6 hours preferred (page 4, lines 25-26). WIPO '135 discloses infusions carried out at suitable intervals of 2 to 4 weeks (page 5, lines 2-3). WIPO '135 discloses the correct dosage of the compounds will vary according to the particular formulation, mode of application, *situs*, host, and tumor being treated (page 5, lines 6-10).

WIPO '135 does not specifically disclose ET-743 administered with a dose range between 0.6 mg/m^2 and 0.75 mg/m^2 and doxorubicin administered with a dose of about 60 mg/m^2 or about 50 mg/m^2 (instant claim 1). WIPO '135 does not specifically disclose the infusion of doxorubicin carried out once every 21 days (instant claim 9). WIPO '135 does not specifically disclose the method wherein the infusion of doxorubicin is carried out on day 1 and the infusion of ET-743 on days 1 and 8, every 21 days (instant claim 10).

van Kesteren et al. teaches ET-743 administered as a 24 hr i.v. infusion every 3 weeks to a human patient with dosage escalation (page 4726, right column, paragraph 5). van Kesteren et al. teaches ET-743 administered at the dosage 400 to $900 \text{ } \mu\text{g/m}^2$, or 0.4 to 0.9 mg/m^2 , results in an increase in plasma concentration that is a predictable trend to one of skill in the art (page 4728, figure 3). van Kesteren et al. teaches ET-743 administered at the specific dosage $600 \text{ } \mu\text{g/m}^2$, or 0.6 mg/m^2 , administered every 21 days during multiple courses (page 4728, right column, section RESULTS). van Kesteren et al. teaches it is known in the art that the dosage for a human in terms of $\mu\text{g/m}^2$ or mg/m^2 can be safely applied at higher dosages than in the mouse model (spanning page 4731, right column, paragraph 4 at bottom and page 4732, left column, paragraph 1 at top).

Takahashi et al. 2001 teaches the effect of ET-743 and doxorubicin is dependent on the sequence of administration of ET-743 and doxorubicin (page 3251, abstract). Takahashi et al. teaches the treatment protocol of ET-743 and doxorubicin administered at a constant molar ratio of 1 ET-743 : 100 doxorubicin (page 3252, left column, Figure

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1 at middle of page). Takahashi et al. 2001 teaches a synergistically additive effect of ET-743 followed by doxorubicin after 24 hrs and a synergistically antagonistic effect of doxorubicin followed by ET-743 after 24 hrs are known in the art (page 3254, right column, paragraphs 1-4). Takahashi et al. 2001 teaches a synergistically additive effect of ET-743 and doxorubicin concomitantly (spanning page 3256, left column, paragraph 4 and right column, paragraph 1), which broadly interpreted is the administration of one agent immediately followed by the other agent.

Dorr et al. teaches dosing guidelines for doxorubicin of 60-75 mg/m² administered every 3 weeks (page 399, table on lines 38-45), or 21 days. Compared to a dose of up to 120 mg/m² (page 399, left column, lines 10-13), a dose of 60 mg/m² is about 50 mg/m².

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine WIPO '135 in view of van Kesteren et al. and in view of Takahashi et al. and further in view of Dorr et al. WIPO '135 teaches the method of combination therapy of ET-743 and doxorubicin to treat the cancer sarcoma in a human. One of ordinary skill in the art would have looked to the prior art van Kesteren et al. for dosage of ET-743 administered as an i.v. infusion every 3 weeks to a human patient to treat the cancer sarcoma and the prior art Takahashi et al. 2001 for the teaches the treatment protocol of ET-743 and doxorubicin administered at a constant molar ratio of 1 ET-743 : 100 doxorubicin concomitantly to treat sarcoma cells. One of ordinary skill in the art would have a reasonable expectation of success in combining WIPO '135 with the dosage taught by in view of van Kesteren et al. and in view of Takahashi et al. because

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van Kesteren et al. teaches that dosage is safe in a human and Dorr et al. teaches that dosage of doxorubicin and administration every 3 weeks is safe in a human. WIPO '135 discloses the correct dosage of the compounds will vary according to the particular formulation, mode of application, *situs*, host, and tumor being treated (page 5, lines 6-10). It would have been routine experimentation for one of ordinary skill in the art at the time of the invention to optimize dosage of the compounds to result in the method wherein the infusion of doxorubicin is carried out on day 1 and the infusion of ET-743 on days 1 and 8, every 21 days.

Response to Applicant's Remarks:

Applicant's Remarks, filed 15 Jan 2009, have been fully considered and not found persuasive in view of the new grounds of rejection of the amended claims.

Applicant's remarks regarding the antagonistic effects between doxorubicin and other agents as supported by evidence provided by, for example, Hahn et al. has been considered. However, Takahashi et al. 2001 teaches ET-743 and doxorubicin administered at a constant molar ratio of 1 ET-743 : 100 doxorubicin concomitantly to treat sarcoma cells and teaches this specific combination exhibits a synergistically antagonistic effect when administration doxorubicin is followed by ET-743 after 24 hrs is known in the art. Concomitant administration, which broadly interpreted is the administration of one agent immediately followed by the other agent, does not result in such antagonistic effects. This teaching by Takahashi et al. 2001 specific to the combination of ET-743 and doxorubicin is more persuasive than general teachings of ET-743 in combination with agents other than doxorubicin or doxorubicin in combination

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with agents other than ET-743. As further evidence, Meco et al. (Cancer Chemother Pharmacol 2003, 52, p131-138, provided by Applicant in IDS mailed 13 Nov 2007) teaches it is known in the art that the ratio of ET-743 to doxorubicin in the combination affects the synergy of the combination determined by a factorial design for the dosages and that the additive advantage is present when the comparative dose of ET-743 is equal to the comparative dose of doxorubicin (page 133, left column, paragraph 5 and page 134, Table 1 at top of page). Meco et al. teaches it is known in the art that the ratio of ET-743 to doxorubicin at a constant molar ratio of 1 ET-743 : 100 doxorubicin is more effective than each drug given alone (page 134, left column, section In vivo studies), or is advantageously additive and safely tolerated by the mouse model. van Kesteren et al. teaches it is known in the art that the dosage for a human in terms of $\mu\text{g}/\text{m}^2$ or mg/m^2 can be safely applied at higher dosages than in the mouse model (spanning page 4731, right column, paragraph 4 at bottom and page 4732, left column, paragraph 1 at top), specifically comparing the 200 $\mu\text{g}/\text{kg}$ toxicity level in the mouse model in Meco et al. (page 134, left column, section In vivo studies).

Regarding the results of the data regarding a reduction in dose-limiting toxicity, Meco et al. provides evidence that this result is not unexpected for the ratio of 1 ET-743 : 100 doxorubicin wherein doxorubicin is administered 1h prior to ET-743 (page 134, right column, paragraph 1). Claim 1 encompasses doxorubicin in a dosage of about 60 mg/m^2 and ET-743 administered in a dosage of 0.6 mg/m^2 . Claims 12 recites doxorubicin in a dosage of about 60 mg/m^2 followed by ET-743 administered in a dosage of 0.7 mg/m^2 . Claim 13 recites doxorubicin in a dosage of about 50 mg/m^2

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followed by ET-743 administered in a dosage of 0.6 mg/m². These dosages are reasonably close enough to the ratio of 1 ET-743 : 100 doxorubicin taught by Meco et al. that one of ordinary skill in the art would expect the same effect of less toxicity for the administration taught by Meco et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Amended Claims 1 and 3-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 19-20 of commonly assigned copending Application No. 11/577,790.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-9 and 19-20 of copending Application No. 11/577,790

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are drawn to a method of treating cancer in a human comprising administering ET-743 and a Pegylated Liposomal form of the anthracycline Doxorubicin. Instant claims 1 and 3-9 are drawn to the method of treating cancer in a human comprising administering ET-743 and doxorubicin. The instant specification discloses one non-limiting embodiment wherein the doxorubicin does not take the form of doxorubicin in the Pegylated Liposomal form (page 8, lines 8-10). However, this disclosure leads one to immediately envision the opposite, the embodiment wherein the doxorubicin does take the form of doxorubicin in the Pegylated Liposomal form. Claims 2 and 3 recites the limitation of instant claim 3. Claim 4 recites the limitation of instant claim 4. Claim 5 recites the limitation of instant claim 5. Claim 6 obviates the limitation of instant claim 6. Claim 7 obviates instant claim 7. Claim 8 obviates instant claims 8 and 9. A dosage of 0.6 mg/m^2 or 0.75 mg/m^2 encompassed within claim 9 of copending Application No. 11/577,790 is rendered obvious by the disclosure at page 14, table 5a of the specification of copending Application No. 11/577,790.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's Remarks:

Applicant's Remarks, filed 15 Jan 2009, have been fully considered and not found persuasive.

As this is not the only remaining grounds of rejection, it is proper to maintain this provisional obviousness-type double patenting rejection.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
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